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Statins and Breast Cancer: Future Directions in Chemoprevention

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Abstract

Given the high incidence, morbidity and mortality associated with breast cancer, developing effective chemopreventive strategies is crucial. Clinicians must carefully identify both populations at risk who would benefit from chemoprevention, and interventions that are effective and safe. Tamoxifen and raloxifene, the two agents approved for breast cancer chemoprevention, and third generation aromatase inhibitors reduce only the incidence of hormone receptor-positive tumors. 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoAR) inhibitors, or statins, are well tolerated and approved for prevention of cardiovascular disease. In preclinical breast cancer models statins carry potent anti-neoplastic activity. Results from epidemiological and clinical studies, however, are conflicting and have not identified a strong relationship between statin use and reduced breast cancer incidence. These studies have several limitations and were not designed to detect modest effects in high-risk populations. Additional focused epidemiological and translational studies in high-risk populations are needed to justify and guide definitive large prospective trials.

Keywords

Statins; HMG-CoAR inhibitors; Breast cancer risk; High-risk populations; Chemoprevention; Cancer recurrence; Biomarkers; Cancer review

Introduction

Due to the high prevalence and morbidity and mortality associated with breast cancer, chemopreventive strategies are needed. Ideally, the development of chemopreventive agents should include pre-clinical studies to demonstrate efficacy, to identify agents that are safe, and to carefully design trials in select populations. Tamoxifen and raloxifene are approved by the Food and Drug Administration (FDA) for breast cancer chemoprevention, but reduce only hormone receptor-positive tumors. Likewise, aromatase inhibitors (AI) reduce the incidence of only hormone receptor-positive tumors in high-risk women. Many agents are currently under investigation for breast cancer prevention, including 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoAR) inhibitors, also referred to as statins.

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Conflict of Interest

Cesar A. Santa-Maria declares that she has no conflict of interest.

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Compliance with Ethics Guidelines

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

In this review we will discuss the rationale and development of chemoprevention in breast cancer, the preclinical and clinical evidence supporting the investigation of statins in this context, and challenges and considerations in further developing statins as chemopreventive agents.

Breast Cancer: Prevalence and Risk Factors

Breast cancer is the most common non-dermatological malignancy diagnosed in women, and is the second leading cause of cancer death in women (1). While the majority of women diagnosed with early breast cancer will survive their disease, most will undergo local and systemic therapies to reduce the risk of recurrence and death. These treatments are associated with transient toxicity and also with long-term morbidity. The estimated cost of breast cancer care in the United States each year is approximately 16.5 billion dollars, more than any other malignancy (2). Therefore, strategies that reduce the risk of breast cancer are greatly needed.

While an average woman in the United States has a 1 in 8 lifetime risk of breast cancer, not every individual has the same risk (1). Important determinants of developing breast cancer include age, family history, genetic risk factors such as BRCA1 and BRCA2 mutations, and hormonal risk factors including early age of menarche, late-onset menopause, nulliparity, late age of first parity, and history of oral contraceptive (OCP) or hormone replacement therapy (HRT) (3,4). Other risk factors include alcohol consumption, obesity, radiation exposure, history of breast biopsies, history of atypical ductal or lobular hyperplasia, lobular or ductal carcinoma in situ, or a personal history of invasive breast cancer (5-8). Data regarding various additional mutations are also emerging as potentially influencing breast cancer risk (9). One of the most common ways of assessing risk is through the Gail Model, which incorporates age, family history, hormonal and other factors (10,11). Knowledge of an individual woman's risk is important when considering chemoprevention strategies.

Current Strategies for Chemoprevention

Based on the effectiveness of adjuvant tamoxifen, a selective estrogen receptor modulator (SERM), in reducing contra-lateral breast cancer risk, several studies have evaluated its role in breast cancer prevention. The National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) P1, and the International Breast Cancer Intervention Study-1 (IBIS-1) investigators found that tamoxifen versus placebo could reduce breast cancer incidence in high-risk populations (12-14). Interestingly, the Italian Randomized Tamoxifen Prevention Trial, which also assessed tamoxifen versus placebo, did not show any reduction in an average-risk population, although an exploratory analysis revealed a favorable effect in high-risk women (15). Tamoxifen's role in breast cancer chemoprevention encouraged investigation of the SERM raloxifene. The Multiple Outcomes of Raloxifene Evaluation (MORE) investigators demonstrated that compared to placebo, raloxifene significantly reduced the risk of breast cancer (RR=0.24, 95% CI 0.13–0.44, $p<0.001$) in postmenopausal women with osteoporosis (16). In P2, NSABP investigators compared the effects of tamoxifen versus raloxifene in women at high-risk, and reported no difference in developing new invasive breast cancer (RR=1.02, 95% CI 0.82–0.28) (17), although long-term follow up favored the tamoxifen arm slightly (RR=1.24, 95% CI 1.05–0.47) [18]. The risk of uterine cancer and thromboembolic events were higher in the tamoxifen-treated group, leading to a preference for raloxifene in postmenopausal women (18). Despite FDA approval of tamoxifen and raloxifene for chemoprevention, uptake in the community has been limited in large part due to concerns of toxicity (19,20).

To assess the role of AIs in breast cancer prevention, the Mammary Prevention.3 (MAP.3) trial investigators compared exemestane to placebo, and reported reduced risk of invasive

breast cancer in high-risk postmenopausal women (RR=0.35, 95% CI 0.18–0.70; p=0.002) (21). Although an increased incidence of serious side effects was not observed, women assigned exemestane overall experienced more hot flashes, fatigue, night sweats, insomnia and arthralgias. Another similar study, IBIS-II, will compare the effects of the AI anastrozole to placebo in high-risk women (22). Of concern, the long-term tolerability of AIs may be a hindrance to clinical utility as AIs were associated with poor tolerance and adherence in adjuvant studies (23).

Importantly, studies of tamoxifen, raloxifene, and AIs have demonstrated a risk reduction of only ER-positive tumors, while an impact on the risk of human epidermal growth factor receptor 2-neu (HER-2/neu) or the triple negative subtypes was not observed. Moreover, none of the studies have demonstrated a survival benefit. Pharmaceuticals currently under investigation for breast cancer prevention include metformin, retinoids, cyclooxygenase-2 inhibitors, bisphosphonates, vitamin D, and statins (24).

Biological Effects of Statins on Cancer

Statins are competitive inhibitors of HMG-CoAR, which affects cholesterol synthesis and are effective in primary and secondary prevention of cardiovascular disease (25-27). Statins are generally well tolerated even when taken over long periods of time, and serious side effects such as hepatotoxicity and myopathies are rare (28,29). Statins are sub-classified as either hydrophilic (such as pravastatin and rosuvastatin) or lipophilic (such as atorvastatin, cerivastatin, fluvastatin, lovastatin and simvastatin) based on tissue selectivity and permeability. Hydrophilic statins are associated with increased affinity to the liver with less systemic absorption, whereas lipophilic statins tend to have increased affinity to peripheral tissues (30).

Statins are associated with reduced cancer-related mortality, explained by a wide array of potential mechanisms of action that may provide biologic plausibility (31). The agents disrupt important signaling pathways in cancer cell proliferation such as the AKT and Ras pathways. Preclinical studies in triple negative breast cancer cell lines demonstrate that statins inhibit DNA binding of nuclear factor kappa beta at the phosphate and tensin homolog promoter, which leads to enhanced phosphorylation of AKT and blocks downstream signaling, and subsequently cell growth inhibition (32). Additionally, by blocking HMG-CoAR, statins shut down the mevalonate pathway and downstream cholesterol precursors such as farnesyl pyrophosphate (FPP) and geranyl pyrophosphate (GPP). Downstream depletion of FPP and GGPP due to statin-mediated inhibition of HMG-CoAR results in failure of the cell to perform post-translational protein prenylation, which can block the function of many proteins in breast cancer cell lines, including Ras, a key enzyme involved in cell signaling survival and proliferation pathways (33-35). Genome-wide analysis has shown that the mevalonate pathway is significantly upregulated in mutant p53, which is present in more than half of all tumors including breast cancer (36,37). Mutant p53 may thus be an important biomarker to help identify tumors sensitive to statins. In triple negative xenograft models expressing mutant p53, simvastatin has been shown to prevent skeletal metastasis (38). Simvastatin is also associated with anti-tumor effects in rodent models possibly through activation of Jun N-terminal kinase, CCAAT/enhancer binding protein homologous protein, death receptor-5 signaling pathway (39,40).

Epidemiology of Statins and Breast Cancer Risk

There are no prospective randomized control trials (RCTs) specifically investigating the effects of statins on chemoprevention of breast cancer, however, several studies have assessed the association between statin use and breast cancer risk. While randomized data

are the gold standard for evaluating efficacy of drugs, well-constructed observational data can be extrapolated to estimate clinical effect in certain cases (41).

Cohort Studies

Most cohort studies have not found an association between statin use and risk of breast cancer, however, these studies have various limitations. Many were designed as large cohorts assessing incidence of various cancers and are limited by incomplete assessment of breast cancer risk factors. These cohorts likely include a large proportion of average-risk women, which could potentially dilute beneficial effects in high-risk populations (42-47).

Canadian investigators assessed breast cancer risk in a cohort of 13,592 statin users and 53,880 non-users and reported that some patients on statins may have an increased risk of breast cancer. Within the statin group, there was a small increase of breast cancer incidence with short-term (1-2 years) use (RR=1.48, 95% CI 1.06–2.07), however, when they restricted the analysis to those using statins for more than 4 years, they observed a reduced risk of breast cancer (RR=0.26, 95% CI 0.12–0.55). While the authors speculated that this discrepancy might be secondary to a combination of small number of cases and surveillance bias, the study is also limited by a short mean follow up (4.2 years), and an excess of HRT use in the statin group (48).

Some studies suggest that the type of statin may be an important factor affecting breast cancer incidence. Using data from women enrolled in Group Health Cooperative, linked to the Surveillance, Epidemiology, and End Results (SEER) database, investigators assembled a cohort of 92,788 women, and stratified analysis by statin class (hydrophilic or lipophilic). They assessed various breast cancer risk factors, but were not able to identify an association between a specific statin and breast cancer risk. The analysis, however, was limited by disproportionately missing data for non-statin users and disease-free women suggesting a difference in screening practice by statin use and disease status (49). In contrast investigators from the Women's Health Initiative reported that, in a cohort of postmenopausal women consisting of statin users and non-users, certain lipophilic statins were associated with an 18% lower breast cancer incidence (hazard ratio (HR) =0.82, 95% CI 0.70–0.97; p=0.02), whereas other statins were not (HR=1.14, 95% CI 0.92–1.42; p=0.24). These findings were observed despite a higher proportion of patients with Gail risk score >1.7% among statin users compared to non-users. Strength of this analysis was that it included important breast cancer risk covariates, and calculated Gail risk scores for individual patients (50). In a recent preliminary update, the authors reported a trend towards an association between lipophilic statin use and decreased breast cancer risk (HR=0.86, 95% CI 0.74–1.00), which was especially noted in simvastatin-users (HR=0.80, 95% CI 0.64–0.99), or in those who used statins for less than 1 year (HR=0.79, 95% CI 0.63–0.99) (51).

Other important factors that may influence the anti-neoplastic effects of statins include host factors. In a prospective observational cohort of elderly women from the Study of Osteoporotic Fractures investigators reported that the use of lipid-lowering medications predicted a significant risk reduction of breast cancer, in particular in those who used statins (RR=0.28, 95% CI 0.09–0.86), after adjusting for some breast cancer risk factors (52). In contrast, in another study that also included an elderly cohort, researchers compared cancer incidence between statin users and glaucoma-medication users as a control arm, but did not find an association between statin use and breast cancer incidence. The study had limited assessment of breast cancer risk factors, short median follow up (2.9 years), and the two groups were slightly unbalanced with statin users having higher body mass index (BMI) and incidence of smoking (53).

Case-control studies

Most case-control studies have not identified an association between statin use and breast cancer. The case-control studies that failed to report an association assessed incidence of several cancers and included either a small percentage of breast cancer patients, or did not adjust for breast cancer risk factors (54-58). Preliminary data from a case-control study investigating 40,421 US female veterans suggested a relationship between statin use and a reduced risk of breast cancer (OR=0.49, 95% CI 0.38–0.62, $p<0.0001$), however, as with many studies, these data are limited by lack of breast cancer risk factor assessment (59).

Conversely, a slightly increased risk for breast cancer was observed in patients identified from the Case-Control Surveillance Study in statin users (OR=1.5, 95% CI 1.0–2.3). This result was driven largely by non-invasive (OR=1.8, 95% CI 0.9–3.6) rather than invasive cancers (OR=1.2, 95% CI 0.7–2.0), and also noted in those taking statins for more than 3 years (60). The authors suggested that detection bias may be a possible explanation for these results, however, the study was also limited by lack of breast cancer risk data. In a follow up report, the incidence of breast cancer in statin users was not increased compared to non-users (OR=1.2, 95% CI 0.8–1.8) (61). Investigators from Washington State reported a slight reduction in breast cancer incidence in a subset of patients who used statins for more than 5 years (OR=0.7; 95% CI 0.4–1.0), suggesting that longer duration may produce favorable effects. Of note, while they did not find an increased incidence of breast cancer between statin users and non-users in their general analysis, statin users had higher BMI (62). These studies suggest that duration of statin exposure may be important, however, how this affects breast cancer incidence is unclear.

As with several cohort studies, a few case-control studies have investigated the relationship of statin type with breast cancer incidence. In a case-control study from the University of Washington, researchers found that the lipophilic statin fluvastatin was associated with reduced breast cancer incidence (OR=0.5; 95% CI, 0.3-0.8), although there was no association with other statins (60). Other studies investigating lipophilic statins and breast cancer incidence have failed to show an association (58).

Randomized Control Trials

While there are no RCTs assessing the role of statins as chemopreventive agents for breast cancer, there are several sub-studies from RCTs assessing cardiovascular endpoints which evaluated incidence of various cancers including breast cancer as pre-specified secondary endpoints. In one study randomizing participants to pravastatin or placebo, new breast cancer was increased in the statin arm (12 versus 1 cases of breast cancer in the statin and control arms, respectively, $p=0.002$). Only 14% of the cohort participants were women, and of the 12 cases of breast cancer in the pravastatin arm, 4 women had a history of breast cancer (one with non-invasive), and one was diagnosed with breast cancer 6 weeks after starting pravastatin (63). A meta-analysis that included 7 RCTs found no association when analyzing the effect of statins on breast cancer risk (fixed-effects model $RR=1.04$, 95% CI 0.81–1.33, random-effects model $RR=1.19$, 95% CI 0.81–1.73) (64). These RCTs had widely variable relative risks and wide confidence intervals all of which involved 1.0, except for the study discussed above (65). Limitations of this meta-analysis of RCTs include heterogeneity of the type and duration of statin use, various follow up intervals, lack of breast cancer risk stratification, and possibly confounding medications. Many patients were also taking drugs that could potentially reduce breast cancer risk, such as aspirin, non-steroidal anti-inflammatory drugs, and metformin. In addition, this population of cardiac patients included a large proportion of patients taking angiotensin converting enzyme inhibitors and angiotensin receptor blockers (66). These agents have been associated with significantly reduced risks of breast cancer when combined with statins, which may have

influenced results (67). Furthermore, the primary RCTs included mainly men, with women representing only 14-52% of the cohorts, and none investigated baseline breast cancer risk. While most of the studies assessed BMI and estrogen use, only two (63, 68) specified menopausal status (only postmenopausal women eligible), and none evaluated Gail-Model risk factors, or other confounding factors that might influence breast cancer risk. Enriching for appropriate sample populations, such as high-risk women, is crucial in detecting clinical efficacy in chemoprevention trials, as illustrated in P1 and P2 (13,17).

Meta-analysis

Two meta-analyses were conducted to investigate the association between statin use and risk of breast cancer (64,69). One group (Bonovas et al.) identified 16 studies that investigated statin use and breast cancer risk from 1993 until 2005 (Table 1) which was updated by other investigators (Undela et al.) who evaluated additional observational studies (Table 1). With over 2.4 million participants, the Undela meta-analysis is the largest study investigating the relationship between statin use and breast cancer risk. Of note, the Undela meta-analysis included one different study, by the same first author, than in the Bonovas meta-analysis (61,70), and included only 21 studies in the final analysis from the 24 studies originally identified. While, neither meta-analysis supports an association between statins and breast cancer risk by random-effects models (Bonovas RR=1.02, 95% CI 0.89–1.18; Undela RR=0.99, 95% CI 0.94–1.04), both studies have several limitations. The Bonovas meta-analysis includes RCTs which were not designed or powered to assess effects on breast cancer risk, and are discussed in the previous section. The Undela meta-analysis is based on observational data alone and includes data that have not been peer-reviewed (two abstracts). Both meta-analyses combine results of various study designs, statin types and drug exposure durations in heterogeneous populations. Neither includes an assessment of breast cancer risk, and presumably included average-risk populations. While authors in both studies conclude that there is no significant association between statin use and breast cancer risk, the limitations of the studies do not allow for the detection of modest, but important effects in high-risk populations.

Studies of Statins in Women with a Known Breast Cancer

The role of SERMs and AIs in prevention was recognized initially from studies conducted in patients with breast cancer. Analyses of statin use in women already diagnosed with breast cancer, therefore, can provide support to further investigate their role in prevention. Additional analysis by the most recent meta-analysis assessed the risk of breast cancer recurrence with statin use (69). The authors analyzed two trials that were not included in the main meta-analysis (n=2,514), and reported that the risk of recurrence was reduced (RR=0.53, 95% CI, 0.37-0.76) in statin users versus non-users (67,71). Another cohort of 18,769 Danish women, not included in the meta-analysis, also found a reduction in the risk of recurrence in breast cancer patients in statin users (adjusted HR=0.80, 95% CI 0.64–1.0), although this was more pronounced in lipophilic users (adjusted HR=0.70, 95% CI 0.53 – 0.92), particularly, in simvastatin users (adjusted HR=0.62, 95% CI 0.46–0.84) (72).

In a preliminary report, investigators from the MD Anderson Cancer Center found that among patients with inflammatory breast cancer statin use was associated with a significant improvement in disease free survival (HR=0.46, 95% CI 0.23–0.69; $p<0.001$), overall survival (HR=0.50, 95% CI 0.31–0.80; $p=0.004$), and breast cancer-specific overall survival (HR=0.47, 95% CI 0.29–0.77; $p=0.003$) (73). While they did not find a difference by statin type, the number of patients using statins was small, and they did not assess other confounding factors. In another preliminary study from the same Center, researchers reported that patients with inflammatory breast cancer who used statins had improved local-regional disease free survival after a median follow up 2.6 years (HR=0.42, $p=0.03$) (74).

Effects of Statin on Biomarkers

While pre-clinical models illuminate biologic plausibility, given the lack of and challenges of obtaining randomized prospective data, understanding biologic effect in human models can provide additional insight into the potential role of statins in breast cancer prevention. Intermediate biomarkers can assist in predicting who may be most likely to benefit from specific interventions. Several models have been proposed to evaluate biomarker modulation including models assessing circulating or tissue-based biomarkers in the healthy breasts of high-risk women, or the contralateral breast of women with a known breast cancer. Another model includes evaluation of biomarkers in women in the pre-surgical setting in a “window-of-opportunity study.” In one such study, researchers assessed the effects of two weeks of atorvastatin on the proliferative index Ki-67 and HMG-CoAR expression between the initial core-needle biopsy and final surgical specimen (75). There was a non-significant average decrease in Ki-67 expression irrespective of HMG-CoAR expression (relative reduction 7.6%, $p=0.39$), however, in tumors where HMG-CoAR was expressed in the initial biopsy, there was a significant decrease of Ki-67 by 24% ($p=0.02$). The study was limited by small numbers ($n=50$) and incomplete data on matched samples, nonetheless, it represents a model that may be used to demonstrate target biomarker modulation in humans.

A recent prospective study evaluated the effects of a 24-28 week course of simvastatin in women with early stage breast cancer after completion of all local therapy and adjuvant chemotherapy (76). Various biomarkers of statin activity and breast cancer risk were investigated including high-sensitivity C-reactive protein (hsCRP), circulating estrogen concentrations, and contralateral breast density. While hsCRP and estrone sulfate were found to be favorably modulated, the trial had a small sample size that included a heterogeneous group of women, and a relatively short duration of statin use. Additional ongoing trials assess the effects of statins on breast cancer risk biomarkers such as histopathologic assessment of breast epithelium using ductal lavage (77,78).

Considerations and Challenges in Developing Statins for Breast Cancer Chemoprevention

The clinical data reported to date do not provide strong association between statin use and breast cancer risk in average-risk women, however, these studies have not specifically investigated high-risk populations, which could hinder the detection of modest effects. Several observational cohort studies have demonstrated reduced risk of breast cancer recurrence in women using statins, which may suggest a role for statins for secondary prevention. When considering prospective prevention trials, women with average-risk may not be the best candidate population. Another important consideration when designing such trials is selection of an appropriate statin. While lipophilic statins have greater systemic affinity than hydrophilic statins, less than 5% of the oral dose reaches systemic circulation in their active open hydroxy-acid form (79). Despite their low systemic concentrations statins can exert systemic biologic effect, which may also be inferred from several clinical studies suggesting that lipophilic statins as having more favorable effects when compared to hydrophilic statins. Of the various lipophilic statins, simvastatin has shown the most evidence of potential efficacy in clinical and pre-clinical studies (32,33,38-40, 80).

In designing future studies, it is important to consider that statins are metabolized in the liver primarily by the cytochrome P450 system, especially CYP3A4, and they interact with the metabolism of several drugs. Given a possible role in secondary chemoprevention, statins may be administered with various hormonal agents. In one study, there was little effect on anastrozole and metabolite following co-administration with simvastatin (81).

Statins may have other potentially beneficial effects in clinical oncologic settings. Propensity-matched cohorts of women undergoing anthracycline-based therapy have shown that women on statins have a lower risk of developing heart failure related hospitalizations than those not on statins (82). In addition, pre-clinical studies suggest that statins may improve bone mineral density, in particular AI-related bone mineral loss (83,84). Statins have also have radio-sensitizing activity in pre-clinical models especially in breast cancer stem-like cells (74). These studies suggest that statins may, therefore, have several important roles in the continuum of breast cancer, as single agents or in combination with standard therapies such as hormonal agents, chemotherapy, or radiation.

Conclusions

While published data suggest that overall there is little or no association between statin use and breast cancer risk in presumably average-risk women, there is compelling evidence from preclinical and some observational studies for possible use of specific statins in breast cancer chemoprevention. Preclinical data have suggested multiple mechanisms for the anti-neoplastic effects of statins, particularly through key cell signaling pathways such as AKT and Ras. Several studies suggest lipophilic statins may have a role in secondary prevention by reducing the risk of recurrence in patients with breast cancer. It is likely that if statins have chemoprevention properties, these may be modest at best, and may be restricted to specific drug type and duration in certain high-risk populations, particular clinical settings, and possibly tumor subtypes. Even if the primary or secondary chemopreventive effects of statins are modest, given the prevalence of breast cancer these agents could potentially benefit thousands of women with a known diagnosis of breast cancer. Since statins are generally well tolerated long-term and are relatively inexpensive, they are attractive chemoprevention agents. Unfortunately, large prospective trials, which would offer more definitive answers, are expensive, require large sample populations, and long-term follow up. Well-designed epidemiological studies in high-risk populations, and translational studies assessing relevant biomarkers, may ultimately justify large-scale RCTs, which could more definitively elucidate the role of statins in primary and secondary breast cancer prevention.

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Table 1
Meta-analyses investigating statin use and breast cancer risk

Meta-analysis	Number of studies	Number of women (number of BC cases, %)	Follow up (years)	Relative risk, 95% CI	Other conclusions
Bonovas et al. 2005 [64]	16 Overall	283,370 (7,859, n/a)	2–15	1.03, 0.93–1.14 ^f 1.02, 0.89–1.18 ^r	No diff between RTC and Observational (Cochran's Q test p=0.12, quantity I ² =30%)
	7 RCTs	17,049 (377, 2.2%)	3–10	1.04, 0.81–1.33 ^f 1.19, 0.81–1.73 ^r	
	9 Observational	266,321 (7,604, n/a)	2–15	1.03, 0.92–1.15 ^f 1.01, 0.88–1.17 ^r	
	4 Cohort	241,862 (4,267, 1.8)	8–15	1.01, 0.79–1.29 ^r	
	5 Case-control	24,459 (3,337, n/a)	2–12	1.00, 0.80–1.25 ^r	
Undela et al. 2012 [69]	24 Overall	2,440,988 (76,759, n/a)	2–15	0.99, 0.94–1.04 [*]	Long term statin use ^{**} RR=1.03, 95% CI 0.96–1.11 Risk of recurrence ^{***} RR=0.53, 95% CI=0.37–0.76
	13 Cohort	2,042,439 (19,250, 0.1)	6–15	1.01, 0.98–1.04 ^r	
	11 Case-control	398,549 (46,575, n/a)	2–14	0.95, 0.84–1.08 ^r	

BC=breast cancer, CI=confidence interval, CVD=cardiovascular disease, f=fixed effects model, n/a not available, r=random effects model, RCTs=randomized control trials, RR=relative risk.

* 21 studies included- excluded 3 with large CI and no effect on final RR: Lovastatin study groups (RR=1.15, 95 % CI 0.37–3.55), Blais et al. (RR=0.67, 95 % CI 0.33–1.38), and Eaton et al. (RR=1.30, 95 % CI 0.70–2.50)

** 10 studies evaluated long term statin used, definition ranged from greater than 3 to 10 years

*** 2 studies evaluated risk of recurrence